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Review

The Importance of Controlling the TGF- β Signaling Pathway in the Gastric Cancer Microenvironment

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Abstract: Gastric cancer is an intractable disease with a high incidence of peritoneal dissemination and obstructive symptoms (e.g. ileus, jaundice, and hydronephrosis) arising from accompanying marked fibrosis. Microenvironmental interactions between cancer cells and stromal cells are the suggested cause of the disease. Transforming growth factor (TGF-β) is an intriguing cytokine exhibiting dual roles in malignant disease, acting as an important mediator of cancer invasion, metastasis, and angiogenesis as well as exhibiting antitumor functions. Moreover, the TGF-β pathway contributes to the generation of a favorable microenvironment for tumor growth and metastasis throughout the steps of carcinogenesis. Among these effects, TGF-β induces the epithelial-to-mesenchymal transition with prometastatic functions, contributes to the conversion of stromal cells to carcinoma-associated fibroblasts, and suppresses the function of immune cells, which compromises the antitumor immune response, leading to cancer progression and stromal fibrosis. In this review, we address the role of the essential TGF-β signaling pathway in the regulation of the activities of components of the tumor microenvironment of gastric cancer and how this contributes to tumor progression and stromal fibrosis. We then explore the potential to optimize therapy that inhibits TGF-β signaling in the preclinical and clinical settings of gastric cancer.

Keywords: TGF-β; gastric cancer; microenvironment

1. Introduction

Gastric cancer is the fourth most common cancer worldwide and the second leading cause of cancer-related death [1]. Peritoneal dissemination is a critical indicator of poor prognosis and represents the most frequent metastatic pattern in gastric cancer [2]. Although clinical outcomes for patients with gastric cancer with peritoneal dissemination have improved with advances in systemic or intraperitoneal chemotherapy, or both, acceptable outcomes have not been achieved [3–6]. Peritoneal dissemination is characterized by the infiltration of cancer cells, and their proliferation is accompanied by extensive stromal fibrosis [7]. These processes contribute to the development of chemoresistance and obstructive disorders such as ileus, obstructive jaundice, and hydronephrosis, which lead to marked deterioration of health-related quality of life. Therefore, new strategies are required for the development of more effective treatment of tumor proliferation and fibrosis associated with peritoneal dissemination of gastric cancer.

Transforming growth factor-β (TGF-β) is a ubiquitously expressed cytokine that mediates or regulates a wide spectrum of biological processes, including proliferation, differentiation, embryonic development, angiogenesis, wound healing, and other functions [8]. Cancer cells generally secrete larger amounts of TGF-β compared with their normal counterparts. In early-stage tumors, the TGF-β pathway promotes cell cycle arrest and apoptosis [9-11], while in advanced tumors; these processes positively associate with tumor aggressiveness and poor prognosis by promoting cancer cell motility, invasion, the epithelial-to-mesenchymal transition (EMT), and cell

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stemness [12]. These findings reveal that the TGF-β pathway enhances or inhibits the malignant phenotype, and this functional switch is called the "TGF-β paradox" [13]. In contrast, at the level of the microenvironment, the TGF-β pathway contributes to the generation of an advantageous environment for tumor invasion and metastasis throughout all steps of carcinogenesis. Therefore, controlling the activity of the TGF-β signaling pathway to develop more effective cancer therapy may be considered primarily as a microenvironment-targeted strategy. Although numerous studies describe the role of TGF-β in the initiation of cancer, highly incisive investigations are required to better understand the function of TGF-β in the tumor microenvironment of gastric cancer.

Our goal was to summarize and discuss the state-of-the-art knowledge of the role of TGF-β in gastric cancer, with special focus on the effects of this cytokine on cells in the cancer microenvironment. Furthermore, we consider how therapeutic strategies aimed at inhibiting TGF-β signaling can impair the peritoneal dissemination of gastric cancer.

2. TGF-β pathway

Numerous excellent reviews extensively cover TGF-β signal transduction [14-17]. Briefly, the TGF-β superfamily comprises more than 30 different members, including the TGF-βs (comprising the three highly homologous isoforms TGF-β1, TGF-β2, and TGF-β), activins, NODAL, bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs), and anti-Müllerian hormone (AMH) [18]. TGF-βs are synthesized as dimeric prohormones and then secreted into the extracellular matrix (ECM). The canonical TGF-β/Smad signaling cascade is initiated when a TGF-β/BMP ligand binds to a type II serine/threonine kinase receptor; and type II serine/threonine kinase receptors, in turn, recruit and phosphorylate type I receptors [19]. Phosphorylated type I receptors subsequently produce a signal by phosphorylating RSmad, which forms a complex with Smad4. TGF-β ligands transmit the signal through Smad2 and Smad3, whereas BMP signaling leads to phosphorylation of Smad1, Smad5, and Smad8 [20]. Activated Smad complexes are transported into the nucleus where they act together with coactivators or corepressors to regulate target gene transcription. Noncanonical TGF-β signaling activates other signaling pathways such as the phosphoinositide 3-kinase-Akt-mTOR pathway, the p38 and Jun N-terminal kinase (JNK) mitogen-activated protein kinase (MAPK) pathways, the small GTPase RhoA and Rac/Cdc42 pathways, and the Ras-Erk pathway. The activation of these pathways enhances tumor growth after canonical TGF-β/Smad signaling is interrupted [21,22].

3. Sources of TGF-β in gastric cancer

3-1 The mechanism of secretion of TGF-β by gastric cancer cells

The sources of TGF-β in tumors vary and include the cancer cells themselves as well as cells of the tumor stroma, with each source leading to context-dependent functional consequences. As indicated above, cancer cells generally secrete larger amounts of TGF-β than their normal counterparts to regulate their own activities within the tumor mass in an autocrine or paracrine fashion [20]. Interestingly, Okazaki et al. demonstrated that the mechanism of secretion of TGF-β by gastric cancer cells involves a local angiotensin II/AT1 receptor-generating system in tumor tissue (Figure 1) [24].

The microenvironment of gastric cancer is approximately pH 5.5 under hypoxic conditions. Gastric cancer cells express trypsinogen that converts to trypsin at pH 5.5 [25]. Furthermore, mast cells that migrate into gastric cancer tissues express tryptase. Trypsin and tryptase generate angiotensin II from circulating angiotensinogen in the absence of angiotensin converting enzyme (ACE) in acidic tissues. Indeed, there is a sharp contrast between tumor tissues and normal regions with respect to the concentrations of angiotensin II in gastric cancer tissue [26]. The angiotensin II type I receptor (AT1R) is highly expressed in gastric cancer cell lines and gastric cancer tissues.

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Angiotensin II has the potential to impair apoptosis induced by NF-κB activation and overexpression and promotes tumor proliferation induced by ERK1/2 activation [26]. Moreover, angiotensin II induces the expression of the TGF-β activator thrombospondin-1 via the AT1 receptor, thereby mediating activation of latent TGF-β [27,28]. The angiotensin II/AT1 receptor axis contributes to fibrosis through endogenous production of TGF-β1 in chronic renal disease [29,30]. Okazaki et al. demonstrated that treatment of MKN45 cells with angiotensin II increases the expression of TGF-β1, whereas pretreatment of cells with angiotensin receptor blockers (ARBs) effectively inhibit this response [24].

3-2. Secretion of TGF-β in the tumor microenvironment

The sustained release of local TGF-β levels is appropriate to maintain normal tissue homeostasis. However, the local secretion of TGF-β from stromal cells and platelets is increased to facilitate tissue repair [31,32]. A similar situation is commonly found in malignant tumors where TGF-β is initially secreted in the microenvironment to control proliferation and cancer progression. Tumors are infiltrated by stromal cells such as fibroblasts, leukocytes, mast cells, macrophages, bone-marrow derived endothelial cells, and mesenchymal and myeloid precursor cells. The presence of these tumor-infiltrating cells is a major source of TGF-β and is thus a suspected source of the accumulation of TGF-β1 at the invasion front of the tumor [33]. Furthermore, the platelet aggregation-inducing factor podoplanin induces the EMT of tumor cells by increasing the release of TGF-β from platelets [34]. In vitro and in vivo analyses reveal that the podoplanin-mediated EMT increases invasiveness, and the tumor cells become resistant to chemotherapy, which is associated with poor prognosis. Local release of TGF-β produces a tumor microenvironment that is conducive to tumor growth, invasion, and metastasis [35].

The TGF-β signaling pathway influences microenvironment fibrosis, angiogenesis, and immune cell infiltration. Activation of the TGF-β pathway induces the EMT, suppressing the function of immune cells that mediate the immune response to tumors, the conversion of fibroblasts to myofibroblasts, and the overproduction of the extracellular matrix, thereby contributing to the maintenance of a favorable tumor microenvironment.

4. The EMT

Abundant evidence reveals the importance of the EMT, in which epithelial cells are transformed into cells with mesenchymal phenotypes characterized by loss of cellular polarity and adhesion as well as enhanced invasive and migratory properties. The components of the complex tumor microenvironment, including tumor stromal cells and cellular factors, modulate the growth of cancer cells and regulate their malignant phenotype through EMT processes induced by diverse intracellular signaling pathways such as those that involve Wnt and receptor tyrosine kinases (RTKs). Better characterized examples of such pathways include Snail [36], Slug [37], zinc-finger E-box binding homeobox 1 (ZEB1/δEF1) [38], zinc-finger E-box binding homeobox 2/Smad interacting protein 1 (ZEB2/SIP1) [39], Twist [40], high mobility group AT-hook 2 (HMGA 2) [41], and forkhead box protein C2 (FOXC2) [42]. Furthermore, an overactive TGF-β-TGF-βR-Smad2 signaling axis could contribute to the establishment of an EMT phenotype by maintaining the epigenetic silencing of epithelial genes [43]. Other signaling pathways are implicated in the TGF-β-induced EMT, including Erk, PI3K/Akt, RhoA, p38-MAPK, and cofilin [23,38,44].

Induction of the EMT is a major mechanism by which TGF-β promotes cell motility, invasiveness, and metastasis of cancer cells [45]. The EMT significantly enhances intravasation of carcinoma-in situ cells through the basement membrane, survival in the circulation, extravasation at distal tissues, and formation of micrometastases in secondary organs [40,46,47]. Furthermore, the EMT is a key driver of gastric cancer progression and induces the migration of gastric cancer cells

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enabling them to reach their metastatic niche through the lymphatic and blood circulatory systems. The EMT phenotype correlates with an advanced stage of gastric cancer [48].

5. Cancer-associated fibroblasts (CAFs) in the microenvironment of gastric cancer

The EMT generates tumor stromal cells, particularly CAFs, which are the most prominent components of the tumor microenvironment in tumor tissues. CAFs secrete factors such as EGF, IGF-1, PDGF, FGF, MMP, and type I collagen that favor malignant progression [49-51], which lead to the deposition of the ECM, the promotion of angiogenesis and the EMT, and the enhancement of proliferation, immunotolerance, and resistance to chemotherapy (Figure 2) [52,53]. These CAF functions play important roles in cancer progression and promote tumor cell invasion and metastasis. CAFs can be isolated from breast, prostate, pancreatic, cholangiocarcinoma, and gastric cancers, which are characterized by abundant fibrotic stroma. Conversely, CAFs are relatively rare in brain, renal, and ovarian cancers [44, 54-61]. A common theory of the origin of CAFs implicates resident tissue fibroblasts where TGF-β may promote the differentiation of fibroblasts to activated fibroblasts [62], which involves chloride intracellular channel 4 (CLIC4) [63]. Genetic ablation of CLIC4 in primary fibroblasts decreases TGF-β-induced expression of α-SMA and other markers, including ECM components.

In turn, CAFs secrete large amounts of TGF-β, which amplify the stromal reaction and induce an autocrine signaling loop that maintains the differentiation of fibroblasts into myofibroblasts [64]. Thus, TGF-β is a key mediator of this dialogue between CAFs and cancer cells. The CAF phenotype is generally distinct from that of normal fibroblasts. For example, Ishimoto et al. reported that the increased expression of RHBDF2, which regulates TGF-β1 signaling is observed in CAFs isolated from human diffuse gastric cancer compared with nonmalignant fibroblasts [65]. There are several theories that propose alternative origins of CAFs, and this topic is still under debate. For example, bone marrow-derived mesenchymal stem cells, hematopoietic stem cells, epithelial cells that undergo the EMT, and endothelial cells that undergo the endothelial-mesenchymal transition are considered possible predecessors of CAFs (Figure 2). In gastric cancer, human peritoneal mesothelial cells (HPMCs) transform into myofibroblast-like cells following exposure to TGF-β, and these cells contribute to stromal fibrosis in a mouse xenograft model when coinoculated with MKN45 gastric cancer cells [66]. Moreover, in vivo experiment demonstrate that bone marrow-derived cells (fibrocytes) migrate and enhance tumor proliferation and fibrosis via the SDF-1/CXCR4 system [67]. These results suggest that HPMCs and fibrocytes have a latent ability to function as CAFs in the gastric cancer tumor microenvironment, which facilitates the development of fibrosis in the primary tumor and peritoneal dissemination (Figure 2).

6. Effect of TGF-β on immune cells

TGF-β is considered one of the most important regulators of proliferation and differentiation of immune cells deposited in a tumor microenvironment. Specifically, TGF-β affects the function of natural killer cells (NK cells), CD4+ and 8+ T cells, macrophages, neutrophils, dendritic mast cells, and B cells. Cytotoxic T lymphocytes (CD8+ CTLs) are required to control tumor progression. CD4+CD25+Foxp3+ regulatory T cells (Treg cells) cells are a specialized T cell subpopulation that suppresses the activation of the immune system [68]. In tumors, natural and adaptive Treg cell concentrations increase in tumor sites and contribute to tumor-induced immunosuppression by suppressing the proliferation and function of CTLs [69]. TGF-β has the capacity to induce FoxP3 gene expression, which drives the phenotypic conversion of naïve T cells to Treg cells [70,71].

Deng et al. found that hypoxia in gastric cancer induces Treg cells in tumors by up-regulating the expression of TGF-β1. Lu et al. found that gastric cancer-induced infiltration of Treg cells predicts poor prognosis of patients with gastric cancer and that some of these Treg cells are converted by TGF-β produced by tumor cells [72]. In B-cells, TGF-β controls the expression of

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immunoglobulins, surface receptors, and major histocompatibility complex type II proteins, which are direct markers of B-cell maturation and differentiation [73]. TGF-β inhibits the proper maturation of NK cells, which then lose their ability to recognize nonself antigens, an important process required for the clearance of cancer cells [74]. Furthermore, TGF-β negatively regulates the ability of dendritic cells to present foreign antigens [75]. Proliferation of the monocyte–macrophage lineage cells is suppressed mainly by TGF-β ligands [76,77].

Two types of macrophages (phenotypes M1 and M2) are present in the tumor microenvironment. Classically activated M1 macrophages can phagocytose tumor cells. Therefore, these macrophages are involved in the immune response against infection and tumor cell invasion. M1 macrophages play a critical role in cellular immunity against cancer. Alternatively activated M2 macrophages perform a function distinct from that of M1 macrophages. M2 macrophages are the most abundant in tumors and are known as tumor-associated macrophages (TAMs) [78], which can facilitate tumor cell proliferation, angiogenesis, and tissue remodeling. Interestingly, Yamaguchi et al. reported that gastric cancer patients with peritoneal dissemination have significantly higher numbers of TAMs with the M2 phenotype in ascites compared with those without peritoneal dissemination [79]. TGF-β activation can induce a shift of polarization from antitumor M1 to M2 TAMs (Figure 2) [80]. Furthermore, TGF-β induces an N2 neutrophil phenotype, which, as well as macrophages, reduces effector function and increases the secretion of inflammatory cytokines [81]. These combined immunosuppressive effects of TGF-β compromise the ability of the host to resist tumor progression and thus serve as a barrier to immunotherapy.

7. Clinical Outlook: Targeting Stromal Modulators of TGF-β in Gastric Cancer

Pharmacological inhibition of TGF-β has been used in preclinical and clinical studies as a strategy to directly hinder tumor progression or modify the tumor microenvironment. Diverse therapeutic agents block the TGF-β pathway, including soluble receptors and antisense oligonucleotides against TGF-β ligands, neutralizing antibodies, and small molecule inhibitors of TGFBRI or II receptors [82]. These TGF-β inhibitors may have limited effects on cancer cells and exert their antitumor activities mainly by affecting TGF-β-responsive cells (fibroblastic, endothelial, and immune cells) in the tumor microenvironment, because TGF-β signaling is altered or absent from cancer cells. Therefore, TGF-β inhibition may be considered to primarily maintain the homeostasis of the tumor microenvironment by down-regulating stromal stimulation by excess TGFβ production by tumor and tumor-related tissues, with an indirect effects on cancer cells.

Numerous studies of preclinical tumor models show that TGF-β inhibitors elicit antitumorigenic effects on several malignancies through microenvironmental changes [35]. Shinto et al. used a mouse model of orthotopically grafted gastric cancer to show that an inhibitor of TGF-β receptor I phosphorylation (Ki26894) suppresses the growth interactions between human scirrhous gastric cancer cells (OCUM-2MLN) and orthotopic fibroblasts and that combination therapy with S1 decreases lymph node metastasis more effectively than S-1 alone [83]. Miao et al. employed mice inoculated with a gastric cancer cell line (SGC-7901) to show that a TGF-β receptor inhibitor (SB-431542) reduces SGC-7901-induced HPMC fibrosis and attenuates the formation of peritoneal dissemination and peritoneal fibrosis [84]. Furthermore, the outcomes of several Phase I and Phase II clinical trials show that therapeutics targeted to TGF-β are safe and efficacious for patients with colorectal, hepatocellular, and non-small cell lung cancer as well as patients with pancreatic ductal carcinoma and other cancers. Many of these trials are in progress [16]. In contrast, clinical trials of TGF-β inhibitors targeting gastric cancer have not been implemented. However, large clinical trial must take into account the ubiquitous expression of TGF-β1 and its receptors and their important roles in maintaining the homeostasis and specialized functions of normal tissues. Therefore, this is a major conceptual problem with the long-term clinical use of these agents, because there is a high likelihood of adverse side effects and the induction of new cancers and autoimmune diseases.

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Certain drugs are widely used in clinical settings that inhibit the TGF-β signaling system. In vivo studies show that repositioning the antihypertensive, angiotensin receptor blocker (ARB) losartan, used at doses that do not affect blood pressure, reduces the expression of TGF-β and decreases the production of stromal collagen and hyaluronan production. Furthermore, losartan reduces interstitial fluid pressure by decreasing the concentrations of ECM components, which contribute to improving the delivery and efficacy of chemotherapeutic agents in orthotopic murine models of orthotropic breast and pancreatic cancer [85]. Okazaki et al. found that the ARB candesartan reduces TGF-β expression and stromal fibrosis through the suppression of an EMT-like change of HPMCs in a mouse xenograft model of gastric cancer [24].

Paclitaxel (PTX), derived from the bark of the Pacific yew *Taxus brevifolia*, is a standard second-line agent for treating advanced gastric cancer. PTX improves intestinal stenosis caused by stromal fibrosis associated with the progression of peritoneal dissemination [86]. Tsukada et al. found that a low dose of PTX suppresses the TGF-β1-induced EMT of HPMCs by inhibiting Smad2 phosphorylation and decreases stromal fibrosis in human peritoneal cells [87].

Protein-bound polysaccharide K (PSK) is isolated and purified from the cultured mycelium of the Basidiomycete *Coriolus versicolor* [88]. PSK is considered a biological response modifier and was approved for use in Japan in combination with chemotherapy to prolong the survival of patients with gastric or colorectal cancer. PSK may inhibit TGF-β signaling through suppression of TGF-β production by binding TGF-β and through acting on TGF-β receptors [89-91]. Ono et al. found that PSK suppresses Smad2 phosphorylation, resulting in the inhibition of the EMT in the colorectal cancer cell line SW837 [92]. Shinbo et al. found that PSK inhibits the EMT-like change of HPMCs in response to TGF-β signaling in vitro as well as the subsequent induction of tumor fibrosis by coinoculation of the gastric cancer cell line OCUM-2MD3 with HPMCs in a mouse xenograft model [93].

Finally, N-[3,4-dimethoxycinnamonyl]-anthranilic acid (tranilast), an orally administered drug with low toxicity, has been used clinically as an antiallergic and antifibrotic agent that inhibits the growth of fibroblasts in keloid tissue [94]. Studies of animal models show that tranilast prevents tissue fibrosis by attenuating local TGF-β 1 expression and subsequent TGF-β-induced collagen deposits in several organs in patients with nonmalignant disorders such as diabetic cardiomyopathy and chronic cyclosporine nephrotoxicity [95, 96]. In a study of gastric cancer, Saito et al. found that tranilast suppresses the TGF-β/Smad pathway by inhibiting Smad2 phosphorylation in HPMCs treated with TGF-β1 and significantly decreases growth and stromal fibrosis in a mouse xenograft model of fibrosis. It is well known that drug repositioning is the application of drugs and other compounds to treat new indications and has been growing in importance during the last few years, accompanied by an increasing number of drugs under development. All of these antihypertensive, anticancer, and antiallergy agents have been widely used in clinical practice without serious side effects and may potentially be safe when administered in combination with TGF-β as tumor microenvironment targeting agents that inhibit gastric cancers.

8. Conclusions

TGF-β signaling is a fundamental pathway required for normal development and the functions of mature cells. TGF-β ligands are widely expressed in all tissues. Moreover, TGF-β is considered a central player during cancer development and progression. The present review explores the role of the TGF-β pathway in the microenvironment of gastric cancer. It is evident that cross-talk between different cells in a tumor microenvironment is essential for cancer progression and that TGF-β is a potent regulator of this cross-talk. TGF-β regulates tumor progression through mutual interactions between various components of the microenvironment such as fibroblasts, HPMCs, stromal cells, and immune cells A special role is recognized for TGF-β-activated CAFs, which represent one of the

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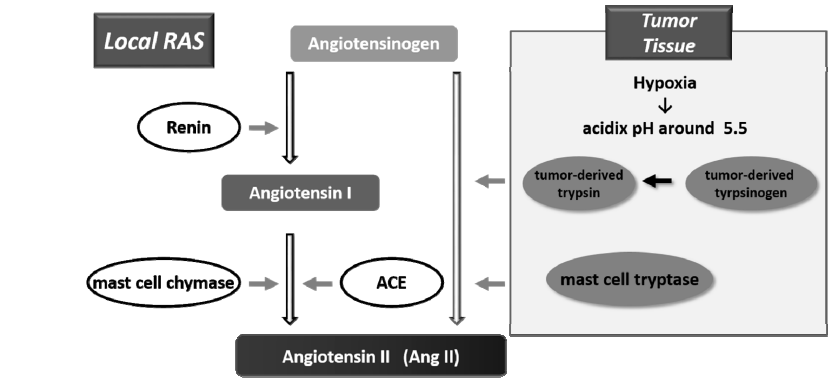
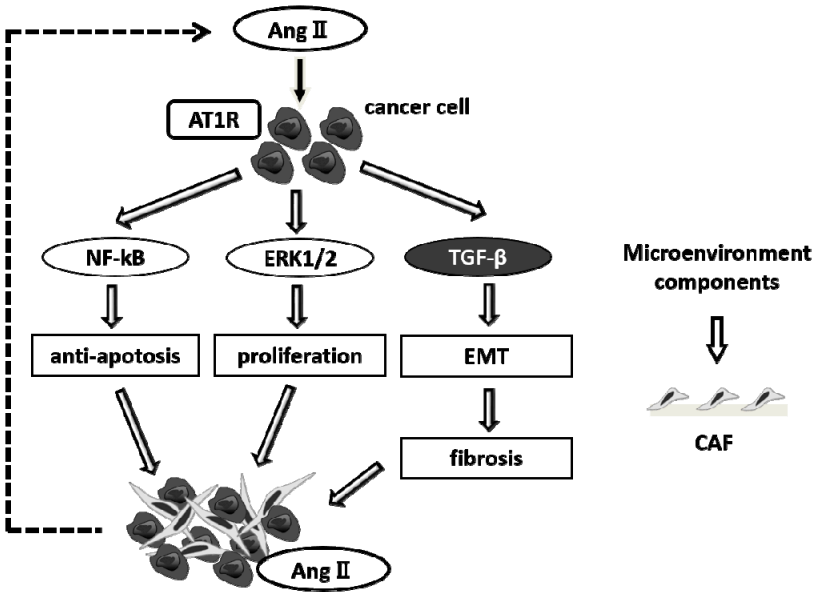
most abundant stromal cell types in virtually all solid tumors. TGF-β–activated CAFs are emerging as a new target for biological therapies of patients with gastric cancer.

It is promising that many anti-TGF-β agents are clinically approved for other diseases (e.g. ARBs, PTX, PSK, tranilast). Repositioning of these drugs can lead to more effective anticancer therapies. Furthermore, the recent development of TGF-β gene expression prognostic tools and TGF-β–response biomarkers may provide the means to select patients for anti-TGF-β intervention to assess effective pharmacological targeting of this pathway. Analysis of the TGF-β signaling pathway in preclinical animal models and human samples has contributed much needed clarity to the role and relevance of TGF-β in human gastric cancer.



(a)



(b)

Figure 1. (**a**) Local angiotensin II generating system in gastric cancer tissue. RAS: renin-angiotensin system, ACE: angiotensin converting enzyme; (**b**) Mechanism of cellular proliferation and stromal fibrosis through angiotensin II/AT1 axis in gastric cancer. AngII: Angiotensin II, AT1R: Angiotensin II type 1 receptor, EMT: epithelial–mesenchymal transition, CAF, cancer-associated fibroblast

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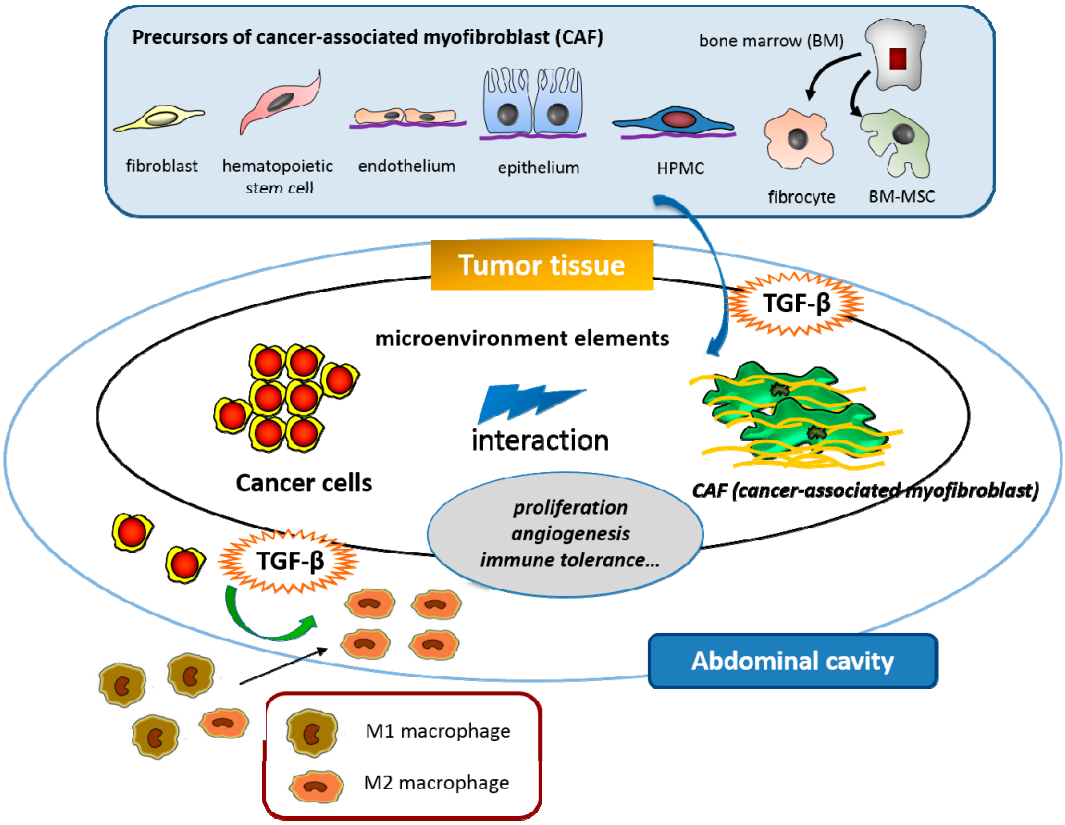

Figure 2. The regulation of TGF-β by the components of the microenvironment of gastric cancer.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

TGF-β	Transforming growth factor-β
EMT	Epithelial-to-mesenchymal transition
CAFs	Cancer-associated fibroblasts
ECM	Extracellular matrix
AT1R	Angiotensin II type I receptor
HPMCs	Human peritoneal mesothelial cells
ARB	Angiotensin receptor blocker
NK cells	Natural killer cells
Treg cells	Regulatory T cells
TAMs	Tumor associated macrophages
PTX	Paclitaxel
PSK	Protein-bound polysaccharide K

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